FILE

UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF THERAPEUTICS RESEARCH AND REVIEW
DIVISION OF CLINICAL TRIAL DESIGN AND ANALYSIS

Memo To: The File, BLA # 97-0201

Subject: Medical Officer's Review, THE EPIC TRIAL 3-YEAR DATA

Reviewer: Dina S. Stolman, M.D., Clinical Reviewer, General Medicine Branch

Through: Marc Walton, M.D., Ph.D., Branch Chief, General Medicine 2/13/98

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Date: February 12, 1998

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1.0 Overview

The evaluation of c7E3 Fab in Prevention of Ischemic Complications (EPIC) trial was the phase 3 clinical trial on which initial marketing approval of Abciximab was based. The findings demonstrated a treatment benefit with Abciximab in high risk patients undergoing PTCA in reduction of ischemic complications at 30 days which was sustained at 6 months. The data presented in this supplement to the original application, PLA 93-1057, present the results of followup of the 2099 patients treated in the EPIC trial at 1, 2 and 3 years post randomization. The sponsors claim a long term benefit is established on the primary endpoint and on secondary endpoints by these data. They propose to modify the package insert to include reference to benefits of treatment sustained at 3 years.

2.0 Proposed Labelling Changes

Two additions are proposed:

1) a claim that benefit on the primary endpoint of the EPIC trial, the composite of death, MI and revascularization, is extended to patients at 3 years

2) statements regarding the interaction of Abciximab with the vitronectin receptor, and a claim that the product more effectively blocks thrombin generation than agents which block platelet gpIIb/IIIa receptors alone.

3.0 Materials Reviewed

Materials included in this review:

- EPIC 3-year Study Report, submitted to BLA 97-0201, dated February 18, 1997
- Sponsor's Responses to Information Requests, dated January 15 and 22, 1998
- Journal article by the EPIC Investigators "Long Term Protection from Myocardial Ischemic Events in a Randomized Trial of Brief Integrin B_3 Blockade With Percutaneous Coronary Intervention", JAMA, 1997; 278:479-484

4.0 EPIC Protocol

4.1 Study Design

The study was a multicenter, multinational, randomized, double blind, placebo controlled parallel arm trial in which 2099 patients were enrolled between November 1991 and November 1992.

4.2 Endpoints

The primary endpoint was a composite of the occurrence within 30 days of all cause mortality, myocardial infarction and urgent revascularization for myocardial ischemia. Secondary endpoints examined each of the components of the primary composite, and the 6 month extension of the primary endpoint. Another secondary endpoint of principal importance included a 6 month composite of all cause mortality, myocardial infarction, and any revascularization procedure (PTCA, STENT, or CABG, including urgent or non-urgent). The incidence of a composite outcome at 6 months including death, MI and revascularization of only the target vessel was also examined.

4.3 Efficacy Findings

A significant treatment benefit was shown on the primary 30 day endpoint (placebo 89/696 (12.8 %), and bolus + infusion 59/708 (8.3 %), a 35 % relative reduction), and this was shown to extend to 6 months. The benefit was primarily in prevention of MI and urgent revascularizations; mortality did not differ between arms. An Agency examination of the data on the 6 month endpoint including all revascularization procedures found a marginal difference on this endpoint; however the reviewers felt the data did clearly demonstrate an extension of the primary endpoint benefit to 6 months.

5.0 Study Methods

5.1 Survey Methodology

The objectives of this study were to evaluate the long-term follow-up of patients in the EPIC trial. Data were obtained on the composite primary and secondary endpoints extended to the 1 year, 2 and 3 year timepoints. The original protocol did not include this long term follow-up; patients were consented a second time for this study.

Patients who had participated in the EPIC trial were contacted by telephone at the 3 year follow up point. They were asked questions regarding their cardiac status from the time of the last (6 month) follow up. Both the patient and the caller were blinded to the patient's treatment assignment until the end of the call. The calls were placed by individuals at the Duke University Coordinating Center.

Medical records were requested for any hospitalizations which had occurred since the 6 month follow up. All medical records were collected by the investigative site or the Duke Cardiovascular Center. They were forwarded to Centocor's Clinical Research Department and then reviewed by an independent blinded Clinical Endpoint Committee, comprised of 4 noninterventional cardiologists and the nursing coordinator at Duke, for adjudication of any cardiac events.

The records, including EKGs, hospital admission and discharge summaries, lab values including CPK/MB's, surgical reports, catheterization and PTCA reports, Emergency Room records, progress, reports, nursing notes, and death or autopsy reports, were reviewed for the incidence of death, MI and revascularizations (PTCA or other PCI or CABG). The CEC reviewers reviewed approximately 2100 cases. EPIC protocol definitions were used to confirm myocardial infarctions. CEC determinations were used for calculation of event rates at the 1, 2, 2.5 and 3 year timepoints.

A location service was used for patients who had moved or could not be located by the Duke Center. For patients whose information was still missing, deaths were checked with the National Death Index at the National Center for Health Statistics. This Index was last queried in December 1994; 62% of patients had reached the 3 year follow up point when this was done.

HACA data were made available to the caller and the patient at the end of the telephone interview, and the patient was unblinded as to the treatment arm he or she had been in. All patients who had positive HACA at the initial (12 week) follow up were asked to have a repeat HACA titer drawn. Samples from the 12 week timepoint were rerun with samples from the 3 year timepoint.

5.2 Statistical Methods

Survival analysis methods were used for data analysis on the primary and major secondary endpoints. Event rates were estimated overall and by treatment group using the Kaplan-Meier method. A generalized logrank test was done for trend across all treatment arms, and pairwise test comparing placebo with each of the treatment arms were performed for each analysis. Analysis of the primary composite endpoint and of components of this composite were based on an Intent-to-Treat population. Other analyses were performed for the ITT population and for treated patients.

Patients were considered to have complete follow-up for an event for a given time interval if the patient was known to have had an event in the interval or if the patient was known not to have had an event by the end of the interval. Patients were censored as of their last date of follow-up. A patient who had an event during the 30 day follow up was considered to have complete 3 year follow up for the composite primary endpoint (*subsequent events for those patients were not captured).*

Proportional hazards modeling was used for subgroup analyses of treatment group effects by diagnostic category at study entry, gender, age, and weight, Type C lesion characteristics, and clinical history of contributing risk factors.

6.0 Study Population

6.1 Completeness of Follow up

Follow-up was quite complete at 1 and 2 years. A total of only 10 patients in the study were actually lost to follow-up at 3 years. A large number of patients had passed the 2.5 year timepoint but not yet reached the 3 year follow-up point, however; only 62 % had complete 3 year follow-up for death and 75 % for MI or revascularization. *(Note: Median follow-up was 3.1 years; for 95 % of the patients, the follow-up ranged from 2.5 to 3.5 years, per data from the sponsor submitted Feb. 2, 1998).*

Event rates at 3 years were estimated by the Kaplan Meier method which censored patients as of the date of their last follow-up. There were no substantial differences across treatment arms at any timepoint in the proportion of patients with complete follow-up. Table 1 presents the patients with complete follow-up at each time point for the placebo and the bolus + infusion arm.

Table 1 Follow Up by Treatment Arm

Death	1 year	2 years	2.5 years	3 years
Placebo (n=696)	694 (99.7)	691 (99.3)	677 (97.3)	440 (63.2)
Bolus + Infusion (n=708)	704 (99.4)	701 (99.0)	689 (97.3)	439 (62.0)
MI or Revascularization				
Placebo (n=696)	669 (96.1)	662 (95.1)	661 (95.0)	528 (75.9)
Bolus + Infusion (n=708)	683 (96.5)	678 (95.8)	678 (95.8)	531 (75.0)

Medical records were requested for all patients who stated during the telephone interview that they had had a hospitalization or procedure during the follow-up period. Overall, 78% of records requested were retrieved (512/660 across all 3 arms of the trial). Records were retrieved for 92 % of cardiac hospitalizations (283/307 across all 3 arms). There was 100 % confirmation of MI's by the CEC. Of the 24 patients whose records for a cardiac hospitalization were not retrieved, there were 7 in the placebo arm and 11 in the bolus plus infusion arm; all involved either PTCA or CABG, and all were counted in the total of procedures in determination of the trial endpoints.

6.2 Baseline Characteristics

The demographic data on patients with and without complete 3 year follow-up is similar. There is a slightly higher percentage of patients without complete 3 year follow-up who had a previous MI; there are fewer who had a previous coronary procedure or > 1 diseased vessel. In addition, an imbalance is reflected in these characteristics between the placebo and the bolus + infusion arm.

Reviewer's Note: The groups are not identical; it is possible these differences may contribute to slightly but not substantially different long-range outcomes in these patients.

Table 2 (next page) shows summary data for the placebo and the bolus + infusion arm patients.

Table 2 Baseline Characteristics

	Patients With 3 year	Complete follow-up	Patients Without 3 year	Complete follow-up
	Placebo n = 528	Bolus + Infusion n = 531	Placebo n = 168	Bolus + Infusion n = 177
Median Age	61	63	59	60
% Male	(72.7)	(71.0)	(74.2)	(72.9)
Median Weight (kg)	85.0	82.0	82.6	81.0
Diabetes	(26.0)	(24.3)	(25.6)	(19.2)
Previous MI	(53.0)	(58.0)	(65.5)	(64.3)
Previous Coronary Procedure	(41.3)	(41.6)	(26.4)	(25.4)
> 1 Diseased Vessels	(47.0)	(47.3)	(40.0)	(34.5)

7.0 Efficacy Results

7.1 Primary Composite Endpoint

Kaplan Meier event rates for the composite endpoint of death, MI or urgent revascularization for clinically significant ischemia are shown for 1, 2, 2.5 and 3 years of follow-up in Table 3.

Table 3 Primary Composite Endpoint Event Rates

Timepoint	Placebo (n = 696)	Bolus + Infusion (n=708)	P value[1]
30 days	89 (12.8)	59 (8.3)	.008
6 months	121 (17.6)	86 (12.3)	.035
1 year	132 (19.2)[2]	103 (14.7)[2]	.025
2 years	149 (21.8)[2]	119 (17.1)[2]	.025
2.5 years	158 (23.2)[2]	129 (18.6)[2]	.03
3 years	165 (24.4)[2]	135 (19.6)[2]	.027

1 Logrank test, 2 sided p values from study report

2 The number of events listed from 1 to 3 years represents the actual number observed; the percentages listed are Kaplan-Meier estimates after patients have been censored as of the date of their last follow-up.

The Kaplan Meier curves for the primary composite endpoint from time of randomization to 3 years follow-up are shown in Figure 1. The prespecified most important secondary endpoint in the EPIC trial was the proportion of patients with endpoint events occurring between 30 days and 6 months. Most of the endpoint events in the trial occurred within the first 48 hours of randomization, and the difference between treatment arms in events occurring after 30 days was not significant. At the time of initial licensing application review, the data were not felt by the Agency to be adequate to support labeling for a separate claim that Abciximab reduced the frequency of endpoint events between 30 days and 6 months. The package insert was approved with a comment that benefit on the primary endpoint was sustained to 6 months.

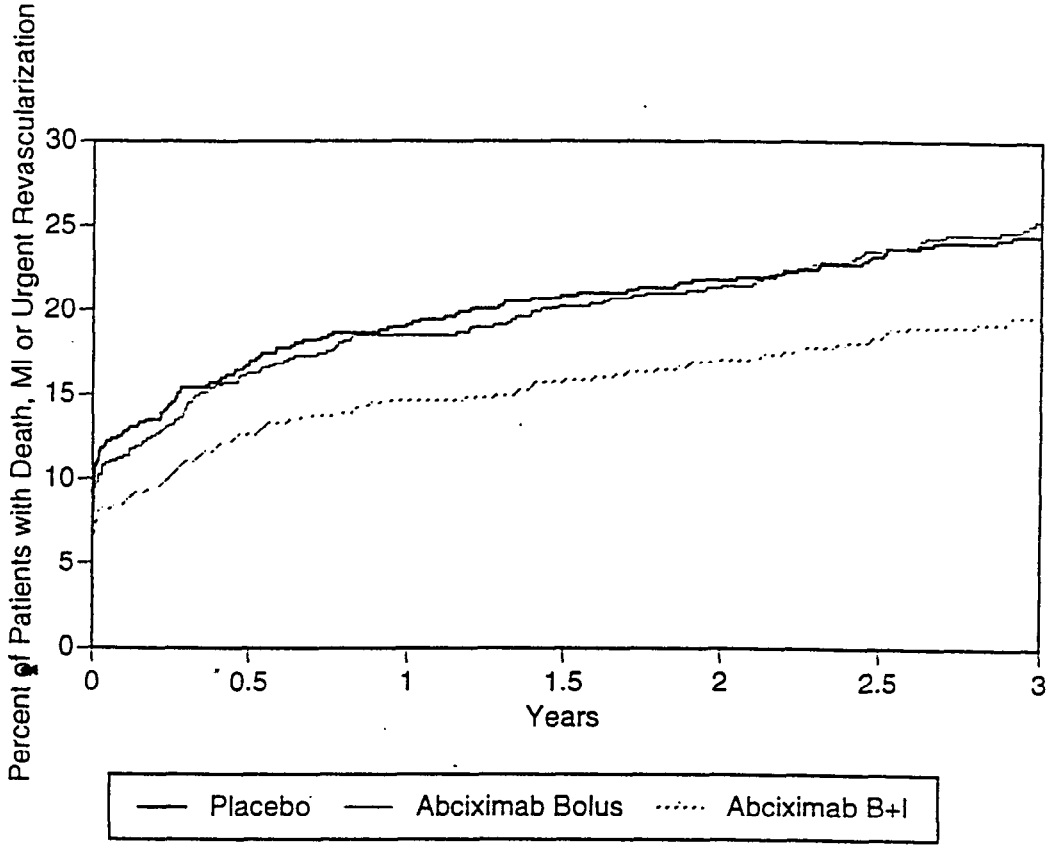


Figure 1

Kaplan-Meier Event Rates for Death, MI and Urgent Revascularization through 3 Years in Randomized Patients.

Because of the marginal significance of the reduction in events between 30 days and 6 months, during this application review the sponsor was asked to provide the rates of primary composite endpoint events at the 1, 2, 2.5 and 3 year timepoints after the events occurring in the first 30 days have been excluded. As can be seen in table 4 below, there does not appear to be additional benefit on the primary endpoint beyond the initial 30 day period.

Table 4 Death, MI or Urgent Revascularization at 1 year through 3 years Excluding Events in 1st 30 days

	Placebo n = 660	Bolus + Infusion n = 644	P value1
1 year	45 (7.6)	44 (6.9)	NS
2 years	62 (10.6)	60 (9.5)	NS
2.5 years	71 (12.2)	70 (11.2)	NS
3 years	78 (13.6)	76 (12.3)	NS

2 Logrank test, 2 sided per sponsor

7.2 Components of the Primary Endpoint

7.2.1 Death

The initial EPIC study report did not detect any difference in mortality between the placebo and the abciximab-treated patients when the 30 day and 6 month data were analyzed (n=23, (3.4 %), placebo, and 22, (3.1%), bolus + infusion at 6 months). The data presented in this submission demonstrate a small numeric reduction in mortality at 2 and moreso at 3 years in the Abciximab-treated patients, that was not statistically significant. The Kaplan Meier curves (Figure 2) converge briefly at 10-12 months, and then diverge to a greater extent beginning at about 1.25 years, and continuing out to 3 years. At the later timepoints, there is close to a 2 % absolute reduction in mortality in the bolus and infusion patients compared to placebo.

Reviewer's Note: Perhaps the patients who initially benefitted from having MI prevented may be able to live longer as a consequence, and there could be a true mortality benefit that is seen late. The numbers are small, however, and statistical significance is not shown.

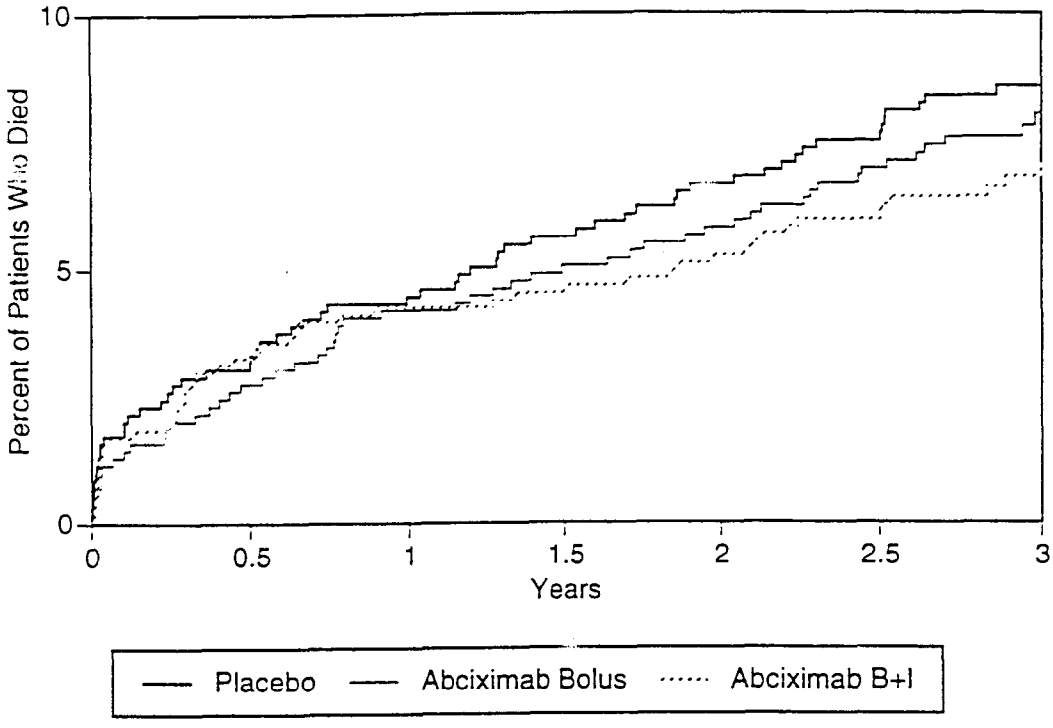


Figure 2

Kaplan-Meier Event Rates for Death through 3 Years in Randomized Patients.

7.2.2 Myocardial Infarction

The reduction seen in the first 30 days in the incidence of MI with Abciximab bolus + infusion appears to be maintained through 3 years follow-up.

Table 5 Myocardial Infarctions at 1 year through 3 years

	Placebo n =696	Bolus + Infusion n = 708	P value[1]
1 year	77 (11.2)	55 (7.9)	.034
2 years	84 (12.4)	64 (9.3)	.058
3 years	91 (13.6)	72 (10.7)	.075

1 Logrank test, 2 sided values per sponsor

7.2.3 Revascularization for Myocardial Ischemia The most frequently occurring endpoint event at all timepoints was revascularization. The sponsor examined all revascularizations and target vessel revascularizations at 1 year through 3 years.

Reviewer's Note: Urgent revascularizations were not presented; this reviewer's calculations show similar rates of urgent revascularizations were observed in the placebo and the bolus + infusion arms at 1, 2 and 3 years.

Table 6 shows the rates of all revascularization procedures at 1, 2, and 3 years. A significant difference is seen between the bolus + infusion and the placebo arms at 1 year, which persists through 2 years and drops off only slightly at 3 years.

Table 6 Total Revascularizations at 1 year through 3 years

	Placebo n =696	Bolus + Infusion n = 708	P value[1]
1 year	221 (32.6)	178 (25.6)	.004
2 years	242 (36.0)	207 (30.2)	.013
3 years	265 (40.1)	234 (34.8)	.021

1 Logrank test, 2 sided values per sponsor

7.3 Secondary Endpoints of Interest

7.3.1 Death, MI and all Revascularizations

When the events in the first 30 days are excluded, there appears to be no difference in the event rates between the placebo and the bolus + infusion treated patients at the later timepoints (see Table 5 below).

Table 7 Death, MI or any Revascularization through 3 years Excluding Events in 1st 30 days

	Placebo n = 551	Bolus + Infusion n = 604	P value1
1 year	129 (23.6)	117 (19.5)	0.08
2 years	153 (28.2)	154 (25.9)	0.45
2.5 years	168 (31.1)	170 (28.7)	0.26
3 years	182 (34.3)	184 (31.5)	0.24

1 Logrank test, 2 sided values per sponsor

7.3.2 Death or MI

The composite including only death and MI appears to show a significant difference out to 3 years (Table 8). However, when the events occurring in the first 30 days are excluded, the difference is no longer significant at timepoints at and past 1 year (Table 9).

Table 8 Death or MI at 1 year through 3 years

	Placebo n = 696	Bolus + Infusion n = 708	P value[1]
1 year	101 (14.7)	76 (10.8)	.06
2 years	121 (17.7)	92 (13.2)	.007
3 years	139 (20.6)	108 (15.8)	.017

1 Logrank test, 2 sided values per sponsor

Table 9 Death or MI at 1 year through 3 years excluding events in 1st 30 days

	Placebo n = 619	Bolus + Infusion n = 660	P value[1]
1 year	33 (5.4)	33 (5.1)	NS
2 years	53 (8.8)	49 (7.6)	NS
2.5 years	63 (10.5)	58 (9.1)	NS
3 years	71 (12.1)	65 (10.4)	NS

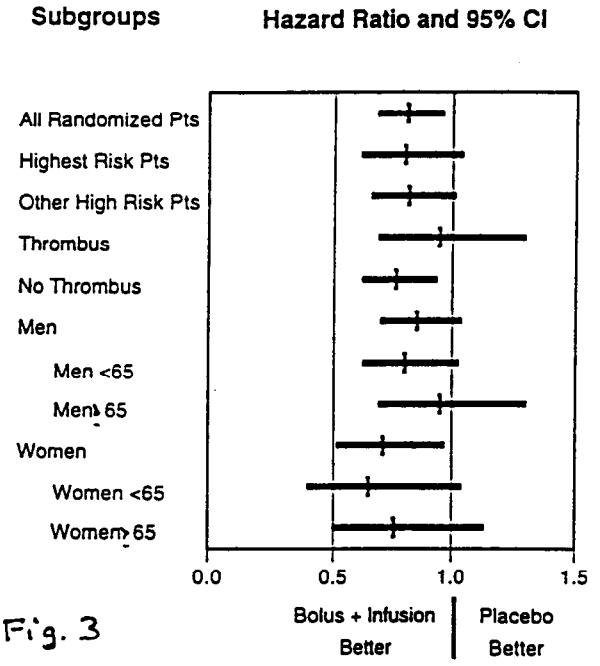
1 Logrank test, 2 sided values per sponsor

7.4 Subgroup Analyses

7.4.1 By Age and Gender There appears to be consistency of abciximab treatment effect across age and gender subgroups, though the patients over age 65 as a whole fare slightly less well than their younger counterparts. Proportional hazards modeling show that all subgroups had better outcomes with treatment than with placebo, at the 3 year timepoint (See Fig 3).

7.4.2 By Diagnostic Category The greatest treatment effects with the ReoPro bolus and infusion were seen in patients with unstable angina or acute MI at study entry, during the first 30 days, as compared to patients with other high risk lesion characteristics, which made up the bulk of the remainder of the study population. This was consistent out to the later timepoints as well, as indicated by the Hazard Ratios below for the 3 year point (see Fig. 3).

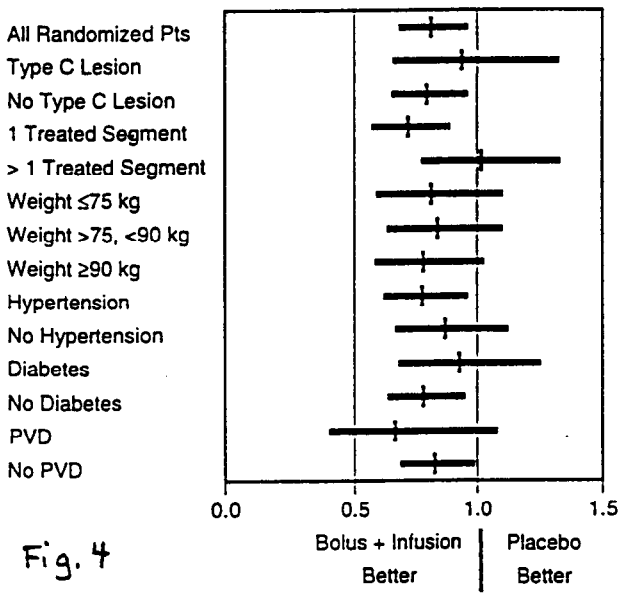
7.4.3 By Predictors of Poor Procedural Outcome When outcomes were evaluated by characteristics known to be independent predictors of a poor procedural outcome, such as Type C characteristics, presence of thrombus, history of diabetes, patients treated with the Abciximab bolus + infusion demonstrated a positive hazard ratio at 3 years (see Fig. 4).



3 Year Endpoint Event Rates			
Placebo		Bolus + Infusion	
n	(%)	n	(%)
696	(47.2)	708	(41.1)
288	(45.3)	299	(39.4)
408	(48.5)	409	(42.3)
216	(37.1)	241	(37.6)
462	(51.0)	440	(42.2)
506	(46.2)	506	(41.9)
340	(44.0)	335	(38.4)
166	(50.5)	171	(48.7)
190	(50.0)	202	(39.1)
87	(50.6)	86	(35.7)
103	(49.8)	116	(41.6)

Fig. 3

Hazard Ratios and the 95% Confidence Intervals (CI) for the Composite Endpoint of Death, MI, and Revascularization through 3 Years Comparing Randomized Patients in the Bolus Plus Infusion Treatment Group and the Placebo Treatment Group in Prespecified Subgroups. All randomized patients are included in this analysis. The number of patients and the 3-year event rates are shown on the right side for each subgroup according to treatment group.



3 Year Endpoint Event Rates			
Placebo		Bolus + Infusion	
n	(%)	n	(%)
696	(47.2)	708	(41.1)
127	(57.4)	111	(54.7)
569	(44.8)	597	(38.5)
458	(44.6)	475	(35.5)
224	(50.7)	214	(52.1)
197	(45.6)	225	(37.7)
234	(48.6)	260	(42.3)
265	(47.4)	222	(42.7)
378	(52.7)	378	(44.6)
318	(40.7)	330	(37.1)
180	(52.8)	163	(51.2)
516	(45.3)	545	(38.0)
59	(63.4)	64	(49.4)
637	(45.8)	644	(40.2)

Fig. 4

Hazard Ratios and the 95% Confidence Intervals (CI) for the Composite Endpoint of Death, MI, and Revascularization through 3 Years Comparing Randomized Patients in the Bolus Plus Infusion Treatment Group and the Placebo Treatment Group in Other Subgroups. All randomized patients are included in this analysis. The number of patients and the 3-year event rates are shown on the right side for each subgroup according to treatment group.

7.4.4 Mortality Overall and in Patients with Unstable Angina and Acute MI at Study Entry

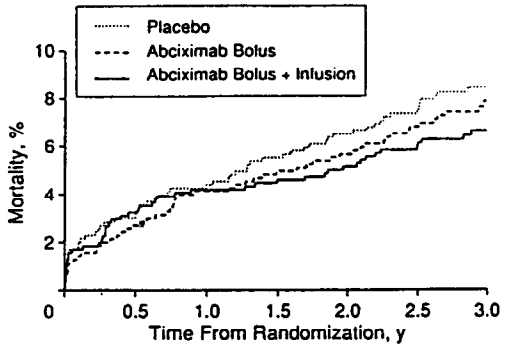
The greatest clinical benefit of treatment was seen in the highest risk subgroups of patients at both early and late timepoints in the study. Patients with unstable angina or acute MI at study entry who were treated with abciximab bolus + infusion actually demonstrated a significant mortality benefit at 3 years compared to unstable angina patients treated with placebo (see Table 10 and Figs. 5 and 6 below).

Table 10 Deaths in Treated Patients Who Had Unstable Angina or AMI at Entry

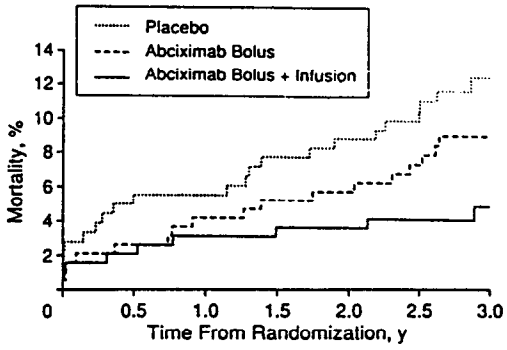
	Placebo n =176	Bolus + Infusion n =178	P value[1]
1 year	10 (5.7)	4 (2.2)	.09
2 years	16 (9.1)	5 (2.8)	.01
3 years	22 (13.0)	7 (4.2)	.003

1 2 sided P value from logrank test per sponsor

Reviewer's Comment: This is a post hoc exploratory subgroup analysis, but does appear to demonstrate a late mortality benefit, particularly in these highest risk patients, but also overall.



Completed Follow-up							
Placebo	696	696	694	692	691	677	440
Bolus	695	695	691	691	688	669	436
Bolus + Infusion	708	706	704	703	701	689	439



Completed Follow-up							
Placebo	179	179	178	178	178	170	101
Bolus	188	188	188	188	187	180	98
Bolus + Infusion	188	188	188	187	187	180	99

Figure 5 & 6. Mortality event curves for overall trial cohort by treatment assignment (left) and mortality for a subgroup of patients with evolving (less than 12 hours) myocardial infarction or unstable angina (right). Reduction in mortality for abciximals bolus + infusion vs placebo had $P=.20$ for entire cohort, but $P=.01$ for the highest-risk subgroup with evolving myocardial infarction or unstable angina.

8.0 Long Term HACA Data

At the time of the (3 year) followup telephone call, patients who had received Abciximab during the trial and who were HACA positive during the initial 12-week monitoring period were asked to return to the lab for an additional HACA measurement. The purpose was to assess the rate and magnitude of persistent HACA positivity at this late timepoint. Samples were available for 34 patients of the 72 HACA positive patients who had received Abciximab in the trial. Samples were drawn between 33 and 49 months after treatment. A positive HACA was seen in 15 of 34 (44 %) of those who had positive titers in the first 12 weeks. Titers ranged from 1:50 to 1:1600 (1 patient). The specificity was to the murine (variable) region in all but 3 patients. Of those three, 2 patients had constant region reactivity. Constant region activity was seen in pretreatment samples in 8% of the EPIC patients.

Reviewer Comment: From this small sample, approximately 40% of those patients who had an initial response to abciximab treatment appear to have a persistent response at 3 to 4 years. The significance of these findings is uncertain, as the persistence of a HACA titer has itself not been demonstrated to have clinical consequences. Data from the Reinjection Registry should provide information on the clinical consequences of patients with positive titers who are retreated with the product.

9.0 Pharmacology Data

The sponsor has included in this submission results of preclinical and clinical pharmacology studies aimed at understanding the sustained benefits seen clinically with Abciximab treatment. The sponsor cites effects on the vitronectin receptor, which mediates endothelial cell proliferation and smooth muscle cell migration. Murine $7E_3$ has been previously characterized as binding to the vitronectin receptor and blocking its functions. The sponsor provides data which demonstrates Abciximab has substantial affinity for various types of human endothelial cells and smooth muscle cells, and that the affinity of $m7E_3$ is similar to that for Abciximab to GPIIb/IIIa on platelets. The sponsor also presents data which demonstrate inhibition of cell spreading, adhesion, migration and proliferation by Abciximab. Additionally, data are presented demonstrating *in vitro* inhibition of thrombin formation on platelets by Abciximab, that is more effective than that seen with antibodies that inhibit either GPIIb/IIIa or vitronectin receptors alone. Thus, the sponsor concludes that Abciximab may be important in inhibiting not only the acute thrombosis of coronary vessels after percutaneous intervention, but the longer term migration and proliferation of vascular smooth muscle cells at sites of vessel wall injury occurring during percutaneous coronary intervention.

The *in vitro* studies are reviewed in greater detail in the Pharmacology Reviewer's (Martin Green, Ph.D.) review.

10.0 Reviewer Discussion and Conclusions

10.1 Study Conduct

This long-term follow-up study was designed and conducted retrospectively, after the initial trial results were known. Follow-up appears excellent, although a large proportion of patients (30-40%) had reached 2.5 years but had not completed the 3 year timepoint at the time of data collection. The number of patients actually lost to follow-up is quite small (10 of 2,099). The use of Kaplan Meier estimates mitigates the effect of the missing data at 3 years. It is unlikely the outcomes would be significantly altered once the full number of patients' data is collected at 3 years.

Patients were questioned regarding the occurrence of endpoint events since completion of the 6 month follow-up . Patients and questioners were blinded; there is no evidence of compromise in the integrity of this process. Data on all cardiac hospitalizations was requested. Retrieval of medical records confirmed the events; the percentage retrieval appears excellent. Events were then verified by a blinded CEC, including 100% of MI's, and most revascularization procedures. There is not a marked difference among treatment arms in the percentage of unretrieved data. Data were not retrieved on every hospitalization for non-cardiac reasons, but it is not likely these would have yielded a significant number of cardiac events (likely incidental) that would have altered the direction or magnitude of the results.

10.2 Efficacy Findings

The long-term follow-up data from the EPIC trial demonstrate a maintenance of the treatment benefit on the composite primary endpoint seen in the first 30 days to 2.5 to 3 years post randomization. The benefit is seen consistently across subgroups by demographic factors, cardiac risk factor history, and presenting diagnosis. Additionally, the Kaplan Meier curves suggest that there may be a long term benefit on mortality; in the first 30 days, the benefits were mainly attributable to prevention of MI and, to a lesser extent, revascularization procedures. These long-term effects are most strikingly demonstrated for patients with MI or unstable angina at study entry, as is true of the benefits seen in the first 30 days. These findings are consistent with the hypothesis that prevention of the acute ischemic complications of percutaneous coronary intervention may result in long term benefit to the patient.

However, when only events occurring after the first 30 days are considered, there is no significant difference between the placebo and the bolus plus infusion treatment arms. No additional benefit is seen, on the composite primary endpoint or any of the components. Such additional benefits would not be anticipated on prevention of MI or of need for revascularization procedures in patients who have received Abciximab only peri-procedural. There is a suggestion of a late benefit on mortality that does not reach statistical significance; this should be examined further with long term follow-up of patients treated with Abciximab in other clinical trials.

This study has also demonstrated that the short term treatment benefits are not overcome by cardiac events in the longer run, and that the occurrence of MI and the need for revascularization are not merely delayed by treatment with Abciximab.

10.3 Labelling Recommendations

<u>Long Term Benefit</u>

The sponsor seeks to add to the present package labelling:

- A statement that the benefit seen on the primary endpoint of the EPIC trial extends to 3 years follow-up.

This reviewer agrees that the statement is supported by the data. A statement regarding the range and the median length of follow-up should be added. This has been discussed with the sponsor, and an agreement reached on acceptable wording.

Vitronectin Data

The sponsor also seeks to add to the label:

- Additional *in vitro* data on the effects of Abciximab on the vitronectin receptor and inhibition of thrombin generation.

The Pharmacology reviewer recommended modification of the text to more specifically reflect the methodology used in the studies cited, and specifically noting that the concentrations used in the thrombin generation study were above the therapeutic range. The sponsor agreed. A disclaimer should be added that the relationship of *in vitro* data to clinical efficacy is uncertain. The sponsor is agreeable this also.

This reviewer recommends approval of the proposed changes to the product labeling for Abciximab based on the items submitted in BLA # 97-0201.